Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c8ob02661k

Received 26th October 2018,
Accepted 18th December 2018

DOI: 10.1039/c8ob02661k

rsc.li/obc

Iron catalysed selective reduction of esters to alcohols†

Sem Raj Tamang, Anthony F. Cozzolino and Michael Findlater *

The reaction of (dppBIAN)$FeCl_2$ with 3 equivalents of *n*-BuLi affords a catalytically active anionic Fe complex; the nature of the anionic complex was probed using EPR and IR experiments and is proposed to involve a dearomatized, radical, ligand scaffold. This complex is an active catalyst for the hydrosilylation of esters to afford alcohols; loadings as low as 1 mol% were employed.

Introduction

Transformation of organic molecules into compounds of increased value, as synthetic intermediates or as final products, is often achieved by employing transition metals as catalysts.[1] In recent years the ability of main group elements,[2] and organocatalysts[3] to effect similar catalytic transformations has also been explored. Although there are many important aspects of catalyst design, recent advances in the rational application of metal–ligand cooperativity have proven highly successful. For example, as a metal center typically undergoes oxidation state changes during catalysis, redox-active ligands assume an increasingly significant role in stabilizing the metal at variety of oxidation states to prevent the degradation of the catalyst.[4]

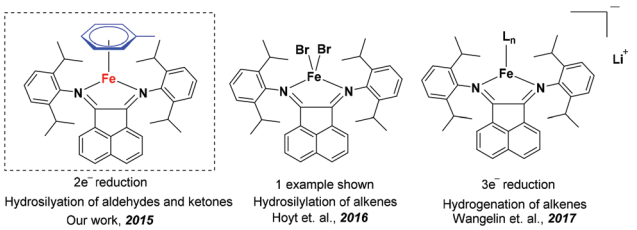
Transition metal catalysis now encompasses a huge range of metals and ligand-types which have been successfully applied in catalysis.[5,4b] One such class is the 'redox non-innocent' ligand; whereby the ligands themselves participate in mediating the catalysis *via* action as either electron donor or acceptor in concert or independently from the metal. This *non-innocence* is useful as oxidation states, which are not common or unconventional, are avoided. Redox non-innocent ligands derived from diimine backbones and complexation with transition metals have been extensively studied and are well documented in the literature.[6] The applications of these complexes in catalysis have shown that reactions that have competing single electron transfer process can now readily and easily catalyze reactions that typically undergo $2e^-$ redox process.[7]

The reduction of carbonyls and their derivatives into alcohols is an important transformation in organic synthesis and has found widespread use in the chemical industry.[8] While, the reduction of aldehydes and ketones to their respective alcohols have been broadly studied and can be achieved under facile and mild conditions, the reduction of esters to alcohols with a broad substrate scope and employing non-precious metals remains a challenge. Typical methods employed in the reduction of esters include hydrogenation,[9] use of strong reducing agents (*e.g.*, $LiAlH_4$, $NaBH_4$)[10] or hydrofunctionalization (*i.e.*, hydroboration,[11] and hydrosilylation[12]). From the perspective of atom-economy, hydrogenation is the most attractive option, but reaction conditions typically employ high pressure and temperature. Metal-catalyzed hydrofunctionalization provides an alternative, and synthetically viable, method to effectively and efficiently reduce esters into alcohols. There are several reports of metal catalyzed hydrosilylation of esters[13] but opportunities exist to improve upon recent progress, especially in the application of earth abundant transition metals as catalysts in this transformation. Moreover, reports of metal complexes involving redox active ligands in the reduction of esters *via* hydrosilyation remain limited,[14] especially in comparison to other transformations where their use is extensive.[15a,7c,15b–d]

Our group has been actively pursuing applications of earth abundant transition metals (M = Fe,[16] Ni,[17] Co[18]) in catalytic hydrofunctionalization chemistry. We have previously reported the syntheses of two ^{dpp}BIANFe complexes: ^{dpp}BIANFeCl_2 and ^{dpp}BIANFe(C_7H_8) (BIAN = 1,2-((bis-2,6-diisopropylphenyl) imino)acenaphthene)[16a] in which the acenaphthene backbone provides a rigid scaffold for the Fe complex (Scheme 1). The latter was found to be active in the hydrosilylation of aldehydes and ketones under solvent and additive free conditions. In 2016, Hoyt and coworkers reported ^{dpp}BIANFeBr_2 which is, after activation with alkali metal salts, capable of the hydrosilylation of 1-hexene (Scheme 1).[19] In 2017, von Wangelin

Department of Chemistry & Biochemistry, Texas Tech University, Lubbock, TX 79409, USA. E-mail: michael.findlater@ttu.edu

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ob02661k



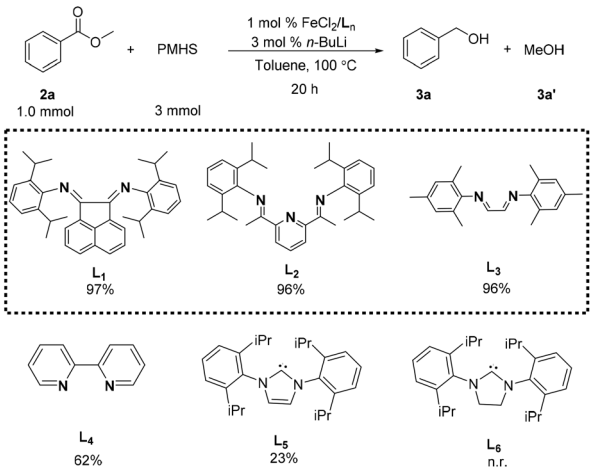
Scheme 1 Examples of ^{dpp}BIAN[Fe] in hydrofunctionalization catalysis.

reported that the addition of 3 equivalents of *n*-BuLi to a solution of ^{dpp}BIANFeCl$_2$ in toluene generated an anionic (but otherwise unknown) [Fe] species which was catalytically active in the hydrogenation of alkenes (Scheme 1).[20] Intrigued by this report, we wondered if a similar approach could be used in the reduction of esters.

Initially, we chose methyl benzoate as a model substrate to explore hydrogenation of esters. Thus, we exposed a reaction mixture of methyl benzoate, 10 mol% ^{dpp}BianFeCl$_2$ and 30 mol% *n*-BuLi in toluene to H_2 at 20 bar pressure; the reaction mixture was heated at 100 °C. Analysis of the reaction mixture by GC-MS after 24 h showed little to no reaction had occurred. Increasing the applied H_2 pressure to 100 bar similarly afforded no reaction. Next, we began to explore hydrosilylation as a reduction method; initially a variety of silanes were screened for activity. Initial screening of the catalytic transformation of methyl benzoate in the presence of silane was performed using 10 mol% ^{dipp}BIANFeCl$_2$, 30 mol% *n*-BuLi, and 3 mmol polymethylhydrosiloxane (PMHS); 100% conversion of methyl benzoate (**2a**) was observed when the reaction mixture was analyzed by GC-MS after 20 h. Lowering the catalytic loading to 1 mol% did not substantially affect catalytic performance as 97% of benzyl alcohol was formed under otherwise identical reaction conditions.[21]

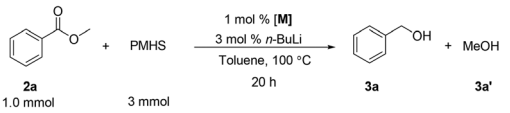
Subsequently, we investigated the influence of different types of redox active (and redox inactive) ligands (Scheme 2). No significant difference was observed employing either PDI (**L$_2$**) or ^{mes}DAB (**L$_3$**) as the supporting ligand. The reactions performed using either FeCl$_2$/**L$_2$** or FeCl$_2$/**L$_3$** afford excellent yields of benzyl alcohol under our optimized reaction conditions. When FeCl$_2$/**L$_4$** (bipyridine) was used as the catalyst, only 62% of benzyl alcohol was formed (Scheme 2). Little to no reaction was observed when redox innocent NHC-based ligands (**L$_5$** and **L$_6$**) were employed. This implies that the electronic nature (redox innocent *vs.* non-innocent) of the ligand may play an important role in facilitating this catalytic transformation. With these results in hand and our prior work with the BIAN (**L$_1$**) framework[16a] we decided to pursue further studies employing MCl$_2$/**L$_1$**.

The effect of changing the metal on catalysis was also tested. Different metal salts, M^{2+} (M = Cu, Mn, Co, and Pd), were complexed with **L$_1$** (Table 1, entries 1–5). Mn showed good activity as the reaction yielded 95% of benzyl alcohol. Interestingly, little to no reaction was observed when complexes of Pd and Cu were used. Commercially available iron



Scheme 2 Ligand effects on catalytic hydrosilylation of methyl benzoate. Yields determined by GC-MS.

Table 1 Optimization with various metals



Entry	[M]	Conversion[a] (%)
1	^{dpp}BIANFeCl$_2$	97
2	^{dpp}BIANCoCl$_2$	44
3	^{dpp}BIANMnCl$_2$	95
4	^{dpp}BIANCuCl$_2$	0
5	^{dpp}BIANPdCl$_2$	0
6	Fe(acac)$_3$	44
7	Fe(OTf)$_3$	0
8	$C_7H_5FeIO_2$	46
9	^{dpp}BIANFe(η^6-C_7H_8)[b]	29

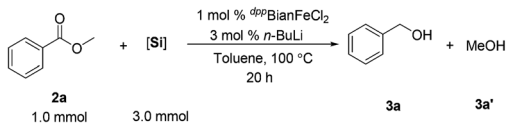
[a] Yields determined by GC-MS employing mesitylene as internal standard. [b] No alkyllithium present.

salts such as Fe(acac)$_3$, Fe(OTf)$_3$ and cyclopentadienyliron dicarboxyl iodide ($C_7H_5FeIO_2$) showed little to moderate activity, and ^{dpp}BIANFe(η^6-C_7H_8) which was previously reported by our group to be highly active in hydrosilylation of carbonyls[16a] yielded only 29% of benzyl alcohol in the absence of *n*-BuLi.

The use of a range of sterically and electronically diverse silylating reagents was examined (Table 2). GC-MS analysis of the reaction mixtures showed excellent conversion of methyl benzoate when phenylsilane and triethoxysilane were used. Moderate activity was observed when 1,1,3,3-tetramethyldisiloxane (TMDS) and diphenylsilane were used as the silylating reagents.

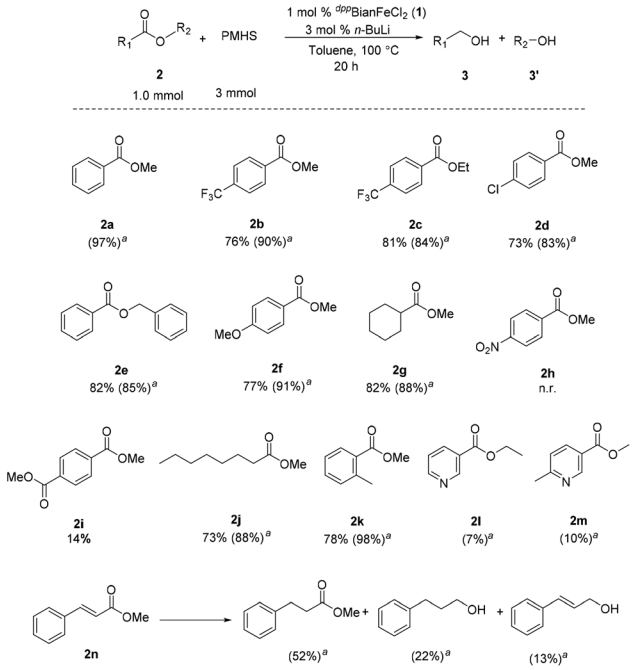
With optimized conditions in hand, we screened a wide variety of esters bearing electron donating, electron withdrawing, and halide substituents, N-heteroarenes, alicylic, and aliphatic esters were also explored in an effort to show the general applicability of our method (Scheme 3). In most cases,

Table 2 Screening of various silylating reagents



Entry	[Si]	Yield[a] (%)
1	PMHS	97
2	Ph_2SiH_2	29
3	$PhSiH_3$	80
4	$(EtO)_3SiH$	85
5	TMDS	54

[a] Based on GC-MS analysis employing mesitylene as an internal standard.

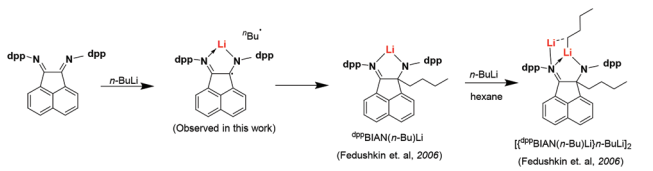


Scheme 3 Substrate scope for hydrosilylation of esters. Isolated yields; [a] values in parentheses represent GC-MS conversion employing mesitylene as an internal standard.

good to excellent isolated yields were obtained except for **2h**, where no reaction was observed. N-Heteroarenes bearing ester substrates showed limited reactivity (**2l**, 7% and **2m**, 10%). Saturation of the α,β double bond was observed for *trans* methyl cinnamate (**2n**); and mixtures of alcohols from hydrosilylation were also observed.

Trovitch and coworkers have recently proposed a mechanism in which a radical transfer and abstraction of H atom occurs in the hydrosilylation of esters in the presence of a manganese catalyst supported by a redox active ligand (PDI); the final silyl ether product arises from the subsequent hydrosilylation of the aldehyde generated *in situ* after β-alkoxide elimination.[14a] In subsequent work, these authors employed detailed experimental and computational analysis to show that radical transfer led to the deactivation of the catalyst.[14b] In an effort to elucidate the mechanistic details in our system, FTIR and EPR studies were conducted. In particular, the role of *n*-BuLi was one we wished to address.

The direct reaction of ^{dpp}BIAN with *t*-BuLi to generate a radical (dearomatized) BIAN backbone has been reported in the literature.[22] Treatment of ^{dpp}BIAN with one equivalent of *n*-BuLi in hexanes or diethyl ether has been reported to give the crystallographically characterized ^{dpp}BIAN(*n*-Bu)Li (Scheme 4).[23] An additional equivalent of *n*-BuLi gives [{^{dpp}BIAN(*n*-Bu)Li}*n*-BuLi]$_2$, which exists as a dimer in the solid state. EPR analysis of a solution of ^{dpp}BIAN in toluene after addition of 1 equivalent of *n*-BuLi revealed an EPR signal with hyperfine coupling ($A_{N\text{-}14}$ = 4.31 G, $A_{Li\text{-}6/7}$ = 3.84/3.87 G) and *g*-factor of 2.003 which implies the presence of an organic radical (Fig. 1) that is perhaps more consistent with a ^{dpp}BIAN radical anion.[24] The paramagnetic nature of this product seems initially at odds with the results of Fedushkin *et al.*[23] The major difference between the two experiments is in the choice of solvent and the concentration. Here, toluene was used, and the concentrations were much lower than those used in the preparation and isolation of ^{dpp}BIAN(*n*-Bu)Li. If the reaction begins with a single electron transfer to the ^{dpp}BIAN ligand, the resulting butyl radical can either react with the ^{dpp}BIAN radical anion, or abstract hydrogen from a solvent molecule. Here, the lower concentration allows for the observation of the presumed ^{dpp}BIANLi radical as shown in Scheme 4. Addition of subsequent aliquots of *n*-BuLi resulted



Scheme 4 Known and proposed reaction pathways of ^{dpp}BIAN with *n*-BuLi.

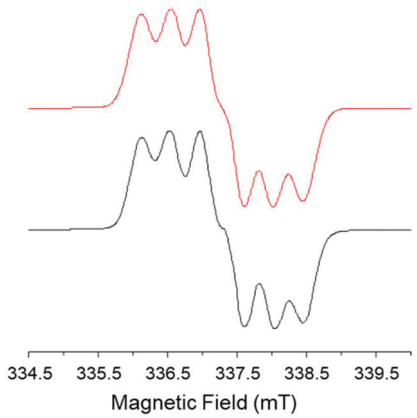


Fig. 1 X-band EPR spectra of ^{dpp}BIAN with 1 eq. of *n*-BuLi in toluene at 298 K. Top: Simulated. Bottom: Experimental.

in a significant decrease in the intensity of the EPR signal (Fig. S1†). Similarly, titration of *n*-BuLi was performed on ^{dpp}BIANFeCl$_2$ and EPR spectra recorded after each addition of *n*-BuLi. ^{dpp}BIANFeCl$_2$ was found to be EPR silent. A weak signal with hyperfine coupling of 4.2 G (*g* factor = 2.003) to two equivalent ^{14}N nuclei was observed when 1 equiv. of *n*-BuLi was added to the reaction mixture. An additional equivalent of *n*-BuLi led to a signal of higher intensity with a broad coupling pattern (Fig. 2). This spectrum can be simulated with the convolution of two EPR active species with *g*-factors of 2.003. The first contains hyperfine coupling to a single ^{14}N (*A* = 4.2 G) and $^{6/7}$Li (*A* = 3.7 G). The second is a broad EPR signal. The signal increases with the addition of the third equivalent of *n*-BuLi (Fig. S2†). The hyperfine coupling remains the same, but the contribution from the species with the broad EPR features increases. A possible model for this could be competing ligand metathesis and complex reduction at each step (Scheme 5).

FTIR data of the sample which was taken upon addition of a stoichiometric amount (relative to the catalyst) of methyl benzoate to the solution after activation of the catalyst with 3 equiv. of *n*-BuLi revealed a change in the stretching mode of the ν_{c-o} band of the ester (Fig. S3 and S4†), and the appearance of a new peak at 1653 cm^{-1} suggesting an interaction of the (now) active catalyst with the ester. This coordination could be presumed to be an initial step prior to the cleavage of the C–O bond. A comprehensive study is currently undergoing in our laboratory to isolate intermediates, and understand the role of the redox active ligand, ^{dpp}BIAN, in the hydrosilyation reactions of esters.

In conclusion, we have shown that hydrosilylation of esters can be achieved upon activation of ^{dpp}BIANFeCl$_2$ with 3 equiv. of *n*-BuLi. Electron donating, electron withdrawing, aliphatic, and alicyclic esters were tolerated and good to excellent reaction yields were observed. Preliminary work suggests the possibility of the involvement of radical transfer in catalysis. Further investigation employing both computational and experimental studies, designed to more fully understand the mechanism, are currently ongoing in our laboratory.

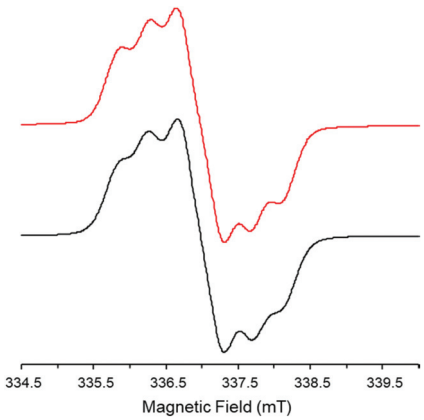
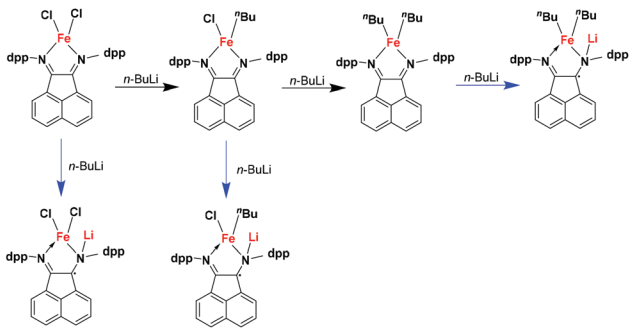


Fig. 2 X-band EPR spectra of ^{dpp}BIANFeCl$_2$ with 3 eq. of *n*-BuLi in toluene at 298 K. Top: Simulated. Bottom: Experimental.



Scheme 5 Proposed reaction pathways of ^{dpp}BIANFeCl$_2$ with *n*-BuLi. Black reaction arrows depict metathesis steps, blue reaction arrows depict complex reduction.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The financial support of the Robert A. Welch Foundation is gratefully acknowledged (Grant No. D1807). Dr Anne-Marie Dechert-Schmitt is thanked for helpful discussions and comments on an earlier draft of this manuscript.

Notes and references

1 (*a*) J. Maes and B. U. W. Maes, in *Adv. Heterocycl. Chem*, ed. E. F. V. Scriven and C. A. Ramsden, Academic Press, 2016, vol. 120, pp. 137–194; (*b*) J. E. Zweig, D. E. Kim and T. R. Newhouse, *Chem. Rev.*, 2017, **117**, 11680–11752; (*c*) J. D. Hayler, D. K. Leahy and E. M. Simmons, *Organometallics*, 2018, DOI: 10.1021/acs.organomet.8b00566.

2 M. S. Hill, D. J. Liptrot and C. Weetman, *Chem. Soc. Rev.*, 2016, **45**, 972–988.

3 J. Alemán and S. Cabrera, *Chem. Soc. Rev.*, 2013, **42**, 774–793.

4 (*a*) H. Grützmacher, *Angew. Chem., Int. Ed.*, 2008, **47**, 1814–1818; (*b*) J. R. Khusnutdinova and D. Milstein, *Angew. Chem., Int. Ed.*, 2015, **54**, 12236–12273.

5 S. Díez-González, N. Marion and S. P. Nolan, *Chem. Rev.*, 2009, **109**, 3612–3676.

6 (*a*) P. J. Chirik, *Inorg. Chem.*, 2011, **50**, 9737–9740; (*b*) D. Zhu, I. Thapa, I. Korobkov, S. Gambarotta and P. H. M. Budzelaar, *Inorg. Chem.*, 2011, **50**, 9879–9887.

7 (*a*) V. Lyaskovskyy and B. de Bruin, *ACS Catal.*, 2012, **2**, 270–279; (*b*) J. I. van der Vlugt, *Eur. J. Inorg. Chem.*, 2012, **2012**, 363–375; (*c*) O. R. Luca and R. H. Crabtree, *Chem. Soc. Rev.*, 2013, **42**, 1440–1459.

8 J. Magano and J. R. Dunetz, *Org. Process Res. Dev.*, 2012, **16**, 1156–1184.

9 (*a*) J. Zhang, G. Leitus, Y. Ben-David and D. Milstein, *Angew. Chem., Int. Ed.*, 2006, **118**, 1131–1133; (*b*) S. Chakraborty, H. Dai, P. Bhattacharya, N. T. Fairweather, M. S. Gibson, J. A. Krause and H. Guan, *J. Am. Chem. Soc.*, 2014, **136**, 7869–7872; (*c*) S. Werkmeister, K. Junge and M. Beller, *Org. Process Res. Dev.*, 2014, **18**, 289–302; (*d*) S. Werkmeister, K. Junge, B. Wendt, E. Alberico, H. Jiao, W. Baumann, H. Junge, F. Gallou and M. Beller, *Angew. Chem., Int. Ed.*, 2014, **53**, 8722–8726; (*e*) S. Elangovan, M. Garbe, H. Jiao, A. Spannenberg, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2016, **55**, 15364–15368; (*f*) J. Yuwen, S. Chakraborty, W. W. Brennessel and W. D. Jones, *ACS Catal.*, 2017, **7**, 3735–3740.

10 J. Seyden-Penne, *Reductions by the Alumino– and Borohydrides in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, 2nd edn, 1997.

11 C. C. Chong and R. Kinjo, *ACS Catal.*, 2015, **5**, 3238–3259.

12 S. Díez-González and S. P. Nolan, *Org. Prep. Proced. Int.*, 2007, **39**, 523–559.

13 (*a*) S. C. Berk, K. A. Kreutzer and S. L. Buchwald, *J. Am. Chem. Soc.*, 1991, **113**, 5093–5095; (*b*) S. C. Berk and S. L. Buchwald, *J. Org. Chem.*, 1992, **57**, 3751–3753; (*c*) Z. Mao, B. T. Gregg and A. R. Cutler, *J. Am. Chem. Soc.*, 1995, **117**, 10139–10140; (*d*) M. Igarashi, R. Mizuno and T. Fuchikami, *Tetrahedron Lett.*, 2001, **42**, 2149–2151; (*e*) S. Das, K. Möller, K. Junge and M. Beller, *Chem. – Eur. J.*, 2011, **17**, 7414–7417.

14 (*a*) T. K. Mukhopadhyay, M. Flores, T. L. Groy and R. J. Trovitch, *J. Am. Chem. Soc.*, 2014, **136**, 882–885; (*b*) T. K. Mukhopadhyay, C. L. Rock, M. Hong, D. C. Ashley, T. L. Groy, M.-H. Baik and R. J. Trovitch, *J. Am. Chem. Soc.*, 2017, **139**, 4901–4915.

15 (*a*) S. Blanchard, E. Derat, M. Desage-El Murr, L. Fensterbank, M. Malacria and V. Mouriès-Mansuy, *Eur. J. Inorg. Chem.*, 2012, **2012**, 376–389; (*b*) A. Quintard and J. Rodriguez, *Angew. Chem., Int. Ed.*, 2014, **53**, 4044–4055; (*c*) P. J. Chirik, *Acc. Chem. Res.*, 2015, **48**, 1687–1695; (*d*) I. J. S. Fairlamb, *Angew. Chem., Int. Ed.*, 2015, **54**, 10415–10427.

16 (*a*) F. S. Wekesa, R. Arias-Ugarte, L. Kong, Z. Sumner, G. P. McGovern and M. Findlater, *Organometallics*, 2015, **34**, 5051–5056; (*b*) A. D. Smith, A. Saini, L. M. Singer, N. Phadke and M. Findlater, *Polyhedron*, 2016, **114**, 286–291; (*c*) S. R. Tamang and M. Findlater, *J. Org. Chem.*, 2017, **82**, 12857–12862.

17 S. R. Tamang, A. Singh, D. K. Unruh and M. Findlater, *ACS Catal.*, 2018, **8**, 6186–6191.

18 S. R. Tamang and M. Findlater, *Dalton Trans.*, 2018, **47**, 8199–8203.

19 M. J. Supej, A. Volkov, L. Darko, R. A. West, J. M. Darmon, C. E. Schulz, K. A. Wheeler and H. M. Hoyt, *Polyhedron*, 2016, **114**, 403–414.

20 M. Villa, D. Miesel, A. Hildebrandt, F. Ragaini, D. Schaarschmidt and A. Jacobi von Wangelin, *ChemCatChem*, 2017, **9**, 3203–3209.

21 Initial optimization revealed a combination of 1 mol% catalyst and 2 mol% *n*-BuLi to be effective in the hydrosilylation of **2a**; however, extension of methodology to various substrates bearing aliphatic, alicylic, and electron donating esters revealed poor to moderate activity (Scheme S1†).

22 (*a*) D. A. Evans and A. H. Cowley, *J. Am. Chem. Soc.*, 2012, **134**, 15672–15675; (*b*) D. A. Evans, I. Vargas-Baca and A. H. Cowley, *J. Am. Chem. Soc.*, 2013, **135**, 13939–13946.

23 I. L. Fedushkin, M. Hummert and H. Schumann, *Eur. J. Inorg. Chem.*, 2006, **2006**, 3266–3273.

24 I. L. Fedushkin, A. A. Skatova, V. A. Chudakova and G. K. Fukin, *Angew. Chem., Int. Ed.*, 2003, **42**, 3294–3298.